REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-76 are in this case. Claims 22-45 were withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention. Claims 1-2, 5, 7, 9-14, 16-17, 19-21 and 46-69 have been rejected. Claims 56-58 and 67-69 have now been canceled. Claims 1, 7, 9-12, 17, 19-21, 46-47, 49-50 and 60-61 have now been amended. New claims 70-80 have now been added.

35 U.S.C. § 103(a) Rejections - U.S. Pat. No. 5,806,529 in view of Bachar-Lustig et al. or Mobest et al. or Vavrova et al.

The Examiner has rejected claims 1-2, 5, 7, 9-14, 16-17, 19-21 and 46-55, 58-66 and 69 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,806,529 in view of Bachar-Lustig *et al.*, or Mobest *et al.*, or Vavrova *et al.* The Examiner's rejections are respectfully traversed. Claims 1, 7, 9-12, 17, 19-21, 46-47, 49-50 and 60-61 have now been amended. Claims 58 and 69 have now been canceled, rendering moot the Examiner's rejections of these claims. New claims 70-80 have now been added.

The Examiner states that the claims are rejected for the same reasons set forth in the Office Action, mailed 12/29/03. In the latter Office Action, the Examiner contended that the '529 patent teaches a method of inducing tolerance to a transplant during bone marrow transplantation comprising administering HPCs from an allogeneic donor, but conceded that this patent does not teach culturing of the HPCs *ex-vivo* under conditions suitable for inducing or enhancing veto activity. The Examiner further contended that Bachar-Lustig *et al.*, Mobest *et al.*, and Vavrova *et al.* each teach culturing of HPCs under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPCs, and for inducing differentiation of said HPCs into CD33+ myeloid phenotype cells using the same culturing conditions as those disclosed in the instant specification. The Examiner additionally contended that Mobest *et al.* and Vavrova *et al.* each teach *ex-vivo* expansion of CD34+ cells that differentiate into CD33+ myeloid phenotype cells offering the possibility of various non-tolerance inducing auxiliary benefits related to

therapeutic transplantation of CD34+ cells. The Examiner concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made that CD34+ HPCs obtained and grown under the conditions putatively taught by any of the secondary reference teachings would be induced to differentiate into myeloid CD33+ cells with the same functional property as HPCs recited in the instant claims absent a showing of unobvious property.

The Examiner further states that Applicant's arguments filed 03/22/04 have been fully considered, but have not been found persuasive.

The Examiner contends that Applicant's arguments are invalid on the basis of Applicant having traversed the primary and secondary references by pointing to the differences between the claims and the disclosure in each reference individually, namely that Applicant argued the references individually and not their combination.

Applicant wishes to respectfully point out that: (i) each of the Examiner's combination rejections is critically based upon the contention that each of the secondary references cited by the Examiner teaches the culturing method of the present invention, and that each such teaching can be combined with teachings of the '529 patent to render the present invention obvious; and (ii) in Applicant's arguments filed 03/22/04, detailed logical arguments were made specifically and clearly demonstrating that none of the secondary references do in fact teach the culturing conditions of the present invention. Thus, by virtue of successfully traversing each pivotal contention upon which each combination rejection is made, Applicant is of the very strong opinion that Applicant's arguments filed 03/22/04 indeed inherently successfully attack and thereby overcome each combination of references cited by the Examiner, in sharp contrast to the Examiner's contentions. Thus, Applicant strongly disagrees with the Examiner's assessment that Applicant's arguments filed 03/22/04 are insufficient to overcome the rejections made by the Examiner in the Office Action, mailed 12/29/03.

Nevertheless, in the interest of expediting prosecution of the instant application, Applicant currently elects to:

(i) Amend each of independent claims 1 and 12 to now recite the limitation of a cultured HPC population having a tolerance-inducing activity, wherein cells displaying a characteristic associated with a myeloid phenotype make up at least 83.5 percent of said HPC population; and the limitation of administering to the recipient a

dose of said cultured HPC population. Specification support for the limitation of a cultured HPC population having a tolerance-inducing activity can be found, for example, in the paragraph starging at page 25, line 17. Clear specification support for the limitation of a cultured HPC population wherein cells displaying a characteristic associated with a myeloid phenotype make up at least 83.5 percent of said cultured HPC population can be found at page 49, sentence starting at line 15 (33% [CD34+CD33+] + 50.5% [CD34-CD33+] = 83.5% [CD33+] total), in combination with page 30, sentence starting at line 1 which indicates that CD33 is a myeloid marker.

(ii) Amend each of claims 9 and 19, depending from claim 1 or 12, respectively, to now recite the limitation of said cultured HPC population being predominantly CD33+. Clear specification support for this limitation can be found, for example, at page 49, sentence starting at line 15.

(iii) Amend each of claims 10 and 20, depending from claim 1 or 12, respectively, to now recite the limitation of said tolerance-inducing activity being enhanced per cell in said cultured HPC population relative to said HPC population derived from the donor. Clear specification support for this limitation can be found, for example, at page 26, sentence starting at line 3.

(iv) Amend claim 50 depending from claim 1; and add New claim 74 depending from claim 12 such that each of these claims now recites the limitation of said characteristic associated with a myeloid phenotype being surface expression of CD33. Clear specification support this limitation can be found, for example, in the paragraph starting at page 29, line 17.

(v) Add New claim 70 depending from claim 1; and amend claim 61 depending from claim 12 such that each of these claims now recites the limitation of said cultured HPC population being characterized by a ratio of at least 7 to 1 of cells displaying said characteristic associated with a myeloid phenotype to cells not displaying said characteristic. Clear specification support for this limitation can be found, for example, at page 31, sentence starting at line 15.

(vi) add New claims 71 and 76, depending from claim 1 or 12, respectively, reciting the limitation of said tolerance-inducing activity being induction of tolerance in cytotoxic T lymphocytes specifically to antigens of said cultured HPC population, wherein said CTLs and said cultured HPC population are allogeneic or xenogeneic

with each other. Clear specification support for this limitation can be found, for example, in the combination of:

(a) the sentence starting at page 22, line 17, which points out that the cultured HPC population possesses veto (tolerance-inducing) activity;

(b) the sentence starting at page 2, line 13, which points out that the veto (tolerance-inducing) activity is induction of recipient tolerance to a transplant from a donor of the veto cells (cultured HPC population);

(c) the first paragraph of page 2, which indicates that the veto (tolerance-inducing) activity is relevant to a recipient to a transplant which are allogeneic or xenogeneic with each other; and

(d) the sentence starting at page 2, line 17, which defines the tolerance-inducing (veto) activity as being specific induction of tolerance (suppression) of cytotoxic T lymphocytes specific for antigens of the cultured HPC population (veto cells).

(vii) Add new claims 79 and 80, depending from claim 1 or 12, respectively, limiting said tolerance-inducing activity to a veto activity.

(viii) Add New claims 72 and 77, depending from claim 1 or 12, respectively, reciting the limitation of said tolerance inducing activity being enhanced per total population in said cultured HPC population relative to said HPC population derived from the donor. Clear specification support for this limitation can be found, for example, at page 26, sentence starting at line 3.

(ix) Add New claims 73 and 78, depending from claim 1 or 12, respectively, reciting the limitation of CD34-negative cells making up at least 50.5 percent of said cultured HPC population. Clear specification support for this limitation can be found, for example, at page 49, sentence starting at line 15).

Thus, the methods claimed by presently amended independent claims 1 and 12, by virtue of being methods of inducing tolerance in a recipient to a non-syngeneic donor-derived transplant via administration to the recipient of a donor-derived cultured HPC population which is composed of at least 83.5 percent cells displaying a characteristic associated with a myeloid phenotype, are clearly not rendered obvious by any of the cited combinations of the primary and secondary references.

Applicant wishes to particularly and respectfully point out that the instant specification teaches for the first time that a cultured HPC population composed of at

least 83.5 percent myeloid cells and of a majority (at least 50.5 percent) of CD34- negative cells not only retains any significant capacity to induce donor-specific tolerance relative to non-cultured HPCs, but further that such capacity is very unexpectedly and optimally enhanced per cell relative to non-cultured HPCs. For preventing donor graft rejection, prior art approaches, in sharp contrast to the teachings of the instant specification, teach administration of purified donor stem cells ('529 patent: abstract, and column 4, paragraph starting at line 43) for achieving transplant tolerance. Thus, Applicant is of the strong opinion that the prior art in fact teaches away from the instantly claimed methods of administering the highly differentiated cultured HPC population of the present invention.

Thus, the surprising findings obtained while reducing the present invention to practice provided for the first time both the means to generate the novel highly differentiated donor-derived cultured HPC population of the present invention, as well as the motivation to administer such a population to a recipient to induce tolerance to a donor-derived transplant.

In view of the above arguments and amendments, Applicant believes to have overcome the 35 U.S.C. § 103(a) rejections.

35 U.S.C. § 112, First Paragraph, Rejections

The Examiner has rejected claims 49, 56-58, 60, and 67-69 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claims 49 and 60 have now been amended. Claims 56-58 and 67-69 have now been cancelled, thereby rendering moot the Examiner's rejections of these claims.

In particular, the Examiner contends that the following quotations represent a departure from the specification and the claims as originally filed, and are not supported by the passages cited by Applicant: "wherein said HPC population derived from the donor is a population of substantially purified CD34+ cells" recited in claims 49 and 60; "wherein the transplant is substantially of non-hematopoietic origin" recited in claims 56 and 67; "wherein the donor is not myelosuppressed or is not potentially myelosuppressed" recited in claims 57 and 68; and "whereas said growth

conditions do not include supplementation with IL-1beta, IL-3, IL-6, and/or IL-11" recited in claims 58 and 69.

In contrast to the Examiner's contentions, Applicant is of the opinion that in fact none of the quotations cited hereinabove represents a departure from the specification and the claims as originally filed, and that in fact the passages cited by Applicant do indeed provide clear support for these quotations.

Nevertheless, in the interest of expediting prosecution of the instant application, Applicant currently elects to amend claims 49 and 69 so as to now recite the limitation of "purified CD34+ cells" instead of "substantially purified CD34+ cells". Clear specification support for the limitation of "purified CD34+ cells" can be found, for example, at page 41, section entitled "Peripheral blood progenitor cell (PBPC) collection, processing and CD34+ purification", sentence starting at line 10 in particular. In the further interest of expediting prosecution of the instant application, Applicant currently elects to cancel claims 56-58 and 67-69, rendering moot the Examiner's rejections of these claims.

In view of the arguments and amendments set forth above, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph, rejections.

35 U.S.C. § 103(a) Rejections - U.S. Pat. No. 5,806,529 in view of Bachar-Lustig et al. or Mobest et al. or Vavrova et al, and further in view of U.S. Pat. No. 6,558,662

The Examiner has rejected claims 56-57 and 67-68 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. No. 5,806,529 in view of Bachar-Lustig *et al.*, Mobest *et al.*, Vavrova et al, as applied above to claims 1-2, 5, 7, 9-14, 17-17, 19-21, 46-55, 58-66 and 69, and further in view of U.S. Patent No. 6,558,662 (hereinafter "the '662 patent"). The Examiner's rejections are respectfully traversed. Claims 56-57 and 67-68 have now been canceled, rendering moot the Examiner's rejection of these claims.

The Examiner contends that the '662 patent teaches a successful method of treating GVHD during transplantation of a transplant transplanted from a donor to a recipient wherein the transplant is of non-hematopoietic origin and wherein the donor is not myelosuppressed.

The Examiner further contends that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of the '662 patent to those of Bachar-Lustig et al or Mobest *et al.* or Vavrova *et al.* and the '529 patent, to obtain the claimed method of inducing tolerance to a transplant or of transplanting a transplant from a donor to a recipient, wherein the transplant is substantially of non-hematopoietic origin, and wherein the donor is not myelosuppressed.

The Examiner yet further contends that one of ordinary skill in the art at the time the invention was made would have been motivated to do so because the '662 patent teaches a successful method of treating GVHD during transplantation of a transplant transplanted from a donor to a recipient wherein the transplant is of non-hematopoietic origin, wherein the donor is not myelosuppressed, and wherein donor stem cells are expanded *ex-vivo* for transplantation. The Examiner states that *ex-vivo* expanded cells can be cultured as taught by Bachar-Lustig *et al.* or Mobest *et al.* or Vavrova *et al.*, and that these *ex-vivo* cultured, amplified and differentiated CD34+ cells can be further used in a method of inducing tolerance to a transplant during bone marrow transplantation taught by the '529 patent. The Examiner further contends that the growth conditions taught by each of the secondary references are the same as those disclosed in the instant specification, and that as such it would have been obvious to one of ordinary skill in the art at the time the invention was made that the CD34+ HPCs obtained and grown under the same conditions as disclosed in the instant specification would also be induced to differentiate into myeloid CD33+ cells with the same functional property as HPCs recited in the instant claims absent a showing of unobvious property.

The Examiner concludes that from the combined teachings of the references that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. The Examiner further concludes that the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant respectfully disagrees with the Examiner's contention that claims 56-57 and 67-68 are, under 35 U.S.C. § 103(a), unpatentable over U.S. Pat. No. 5,806,529 in view of Bachar-Lustig *et al.*, Mobest *et al.*, Vavrova et al, as applied

above to claims 1-2, 5, 7, 9-14, 17-17, 19-21, 46-55, 58-66 and 69, and further in view of the '662 patent.

Applicant wishes to respectfully point out that the '529 and '662 patents are limited to teaching administration of (preferably purified) donor stem cells (i.e. CD34+ cells; refer, for example, to: '529 patent: abstract, and column 4, paragraph starting at line 43; and descriptions of each aspect of the '662 patent: first aspect, column 1, second-to-last paragraph; second aspect, column 3, second-to-last paragraph; third aspect, column 4, paragraph starting at line 42; and fourth aspect, column 4, paragraph starting at line 49). The '662 patent defines "stem cells" as cells which are "capable of developing into all myeloid and lymphoid lineages" (i.e. CD34+ cells; column 6, paragraph starting at line 17). In sharp contrast to the instant specification, at no point does the '662 patent refer to, imply or in any way teach administration of a highly differentiated cultured cell population composed of a very large majority of myeloid cells (at least 83.5 percent CD33+), and a majority (at least 50.5 percent) of CD34-negative cells, in sharp contrast to the instant specification which indeed does teach administration of such a cell population for inducing transplant tolerance (for example, specification, page 49, sentence starting at line 15). It is further made clear in the "Overview" section of the '662 patent (in particular column 5, sentence starting at line 56) that the '662 patent exclusively teaches a method of administering bone marrow cells in the absence of resultant graft-versus-host effects (i.e. GVHD). In critically opposite contrast, however, the present invention teaches administration of cultured HPCs in the absence of resultant host-versus-graft effects (i.e. graft rejection), which, it will be appreciated that, are clearly immunologically distinct from, and the converse of, graft-versus-host effects. Still further, with respect to *ex-vivo* culturing of stem cells, the '662 patent is limited to teaching ex-vivo expansion of stem cells for transplantation (refer, for example, to column 3, first sentence), and at no point ever refers to, implies, or in any way teaches *ex-vivo* culturing of donor stem cells to generate a highly differentiated cultured cell population for transplantation which is composed of at least 83.5 percent myeloid cells, and which includes a majority of CD34-negative cells for transplantation, in sharp contrast to the instant specification which does in fact teach such a novel highly differentiated cultured cell population (specification, page 49, sentence starting at line 15). As such, Applicant is of the very strong opinion that the '662 patent in fact

clearly and vigorously teaches away from administering in the context of donor graft transplantation a highly differentiated cultured HPC population such as that taught by the instant specification. Therefore, on the basis of the arguments provided hereinabove, as well as on the basis of the arguments provided above in response to the 35 U.S.C. § 103(a) rejections based on U.S. Pat. No. 5,806,529 in view of Bachar-Lustig *et al.* or Mobest *et al.* or Vavrova et al, Applicant is of the very strong opinion that one of ordinary skill in the art would clearly not have had a reasonable expectation of success in producing the claimed invention from the combined teachings of the references. Concomitantly, Applicant is of the very strong opinion that the invention as a whole was not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Nevertheless, in order to expedite prosecution of the present application, Applicant currently elects, as described hereinabove, to cancel claims 56-57 and 67-68, rendering moot the Examiner's rejections of these claims.

In view of the above arguments and amendments, Applicant believes to have overcome the 35 U.S.C. § 103(a) rejections.

Applicant wishes to point out that no new matter has been introduced in the claims filed in the present communication, above.

Statement of Substance of Interview

This statement of substance of interview is made pursuant to the telephone interview of September 14, 2004, and further in response to the Interview Summary from the USPTO mailed September 15, 2004. The interview participants were Michail A. Belyavskyi, Prof. Yair Reisner, Gal Ehrlich and Sol Sheinbein. All claims were discussed. The prior art discussed during the interview was: U.S. Patent No. 5,806,529; Bachar-Lustig *et al.* (Blood, 1999, v. 94, pp 3212-3221); Mobest D. *et al.* (Biotechnology and Bioengineering, 1998, v.60 pp. 341-347); and Vavrova *et al.* (Hematol Cell Ther. 1999, v.41, pp 105-112). The Examiner states that the substance of the interview comprised Applicant's consideration of amending the claims to specifically recite the growth conditions, the ration of the administered cells, and their veto activity; and provision of a declaration by Prof. Reisner stating the novelty of administering veto cells to an allogeneic patient.

Applicant respectfully disagrees with the Examiner's specific phrasing with

respect to the substance of the interview involving Applicant considering amending the claims to "*specifically recite the growth conditions*". Applicant is respectfully of the opinion that it would be more accurate to characterize the substance of the interview as involving Applicant's consideration of amending the claims to specifically recite growth conditions suitable for generating the novel and non-obvious cutured HPCs of the present invention. In accordance therewith, and as described above, independent claims 1 and 12, from which all instantly filed claims depend, have now been amended to recite growth conditions which are specifically suitable for generating a cultured HPC population which is made up of at least 83.5 percent cells displaying a characteristic associated with a myeloid phenotype.

Applicant respectfully disagrees with the Examiner's specific phrasing whereby the substance of the interview involved consideration by the Applicant to amend the claims to specifically recite "*the ration of administered cells*". Applicant is respectfully of the opinion that it would be more accurate to characterize the substance of the interview as involving Applicant's consideration of amending the claims to specifically recite administered cells as defined by their novel and non-obvious structural/functional attributes. In accordance therewith, claims 1 and 12 have now been amended to recite administration of a cultured HPC population having tolerance-inducing activity and being made up of at least 83.5 percent cells displaying a characteristic associated with a myeloid phenotype.

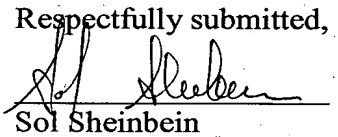
Applicant agrees with the Examiner's statement that the substance of the interview involved consideration by Applicant to specifically amend the claims to recite the veto activity of the cells. In accordance therewith Applicant currently elects to amend claims 1 and 12 to now recite a cultured HPC population having a tolerance-inducing activity, and to add new claims 71 and 76, depending from claims 1 and 12, respectively, which limit said tolerance-inducing activity being induction of tolerance in cytotoxic T-lymphocytes specifically to antigens of said cultured HPC population, wherein said CTLs and said cultured HPC population are allogeneic or xenogeneic with each other. As is described in the passages of instant specification referred to in Applicant's response to the outstanding 35 U.S.C. § 103(a) Rejections (U.S. Pat. No. 5,806,529 in view of Bachar-Lustig *et al.* or Mobest *et al.* or Vavrova *et al.*), such tolerance-inducing activity is veto activity. Further in accordance therewith, Applicant currently elects to add new claims 79 and 80, depending from claims 1 and 12,

respectively, which limit said tolerance-inducing activity to veto activity.

Applicant respectfully disagrees with the Examiner's specific phrasing whereby the substance of the interview involved consideration by Applicant to provide a declaration by Prof. Reisner stating the novelty of administering "veto cells" to an allogeneic patient. Applicant is respectfully of the opinion that it would be more accurate to characterize the substance of the interview as involving Applicant's consideration to provide a declaration by Prof. Reisner stating the novelty of administering to an allogeneic patient a donor-derived graft concomitantly with a cultured donor-derived HPC population having tolerance-inducing activity and being made up of at least 83.5 percent cells displaying a characteristic associated with a myeloid phenotype. In accordance, therewith, such a declaration is enclosed with the present response.

In view of the amendments and remarks set forth above it is respectfully submitted that claims 1-2, 5, 7, 9-14, 16-17, 19-21 and 46-55, 59-66 and 70-80 are now in condition for allowance. Prompt Notice of Allowance is respectfully and earnestly solicited.

Respectfully submitted,



Sol Sheinbein
Registration No. 25,457

Date: October 25, 2004

Encl.:
A 3-months extension fee;
A response transmittal fee for added claims;
A declaration by Prof. Yair Reisner;
Article of Bock TA. *et al.*, 1999. Bailliere's Clinical Haematology Vol. 12, Nos 1/2; and
Abstract of Kaufman *et al.*, 1994, Blood 84:2436-2446.